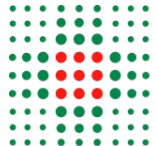


NET MDT: Endoscopic Techniques



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SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Ferrara

Gastroenteropancreatic NETs

Focus on: Well differentiated NETs

Gastroenteropancreatic (GEP) NENs arise from either the tubular gastrointestinal tract or the pancreas.



Well-differentiated NETs of the tubular gastrointestinal tract are often well-circumscribed lesions in the submucosa or extending to the muscular layer, while those that arise in the pancreas may be well-circumscribed, multinodular, or infiltrative.

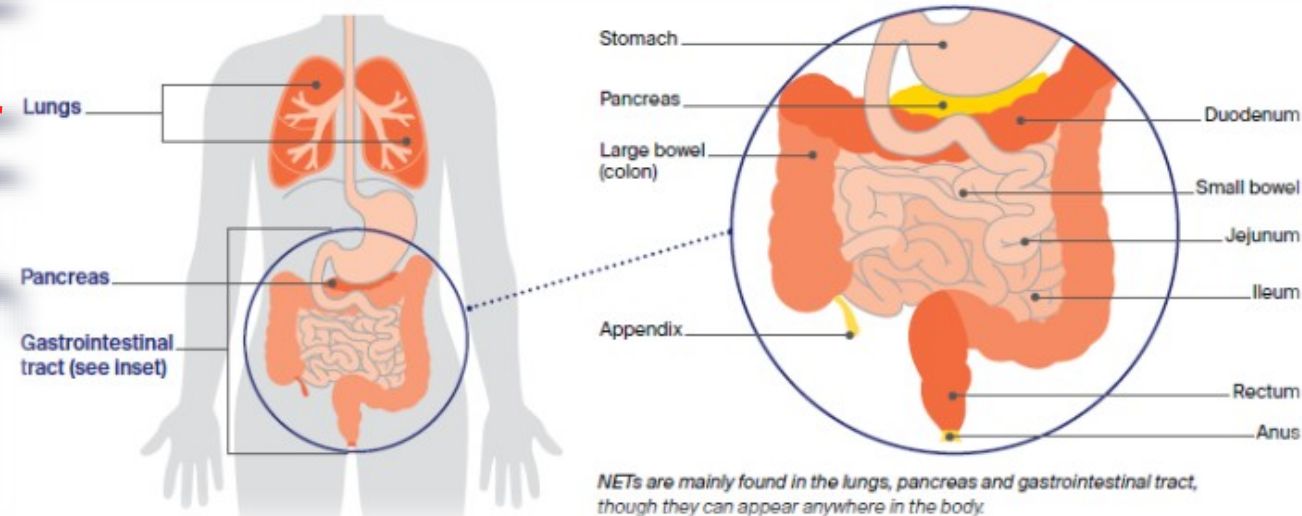
Gastroenteropancreatic NETs

Staging system

Ninth version of the combined American Joint Committee on Cancer/Union for International Cancer Control tumor, node, metastasis staging system.

- **NETs of the appendix**
- **NETs of the jejunum and ileum**
- **NETs of the duodenum and ampulla of Vater**
- **NETs of the colon and rectum**
- **NETs of the stomach**
- **Pancreatic NETs**

Where are NETs mainly found?



Gastroenteropancreatic NETs

The Role of Endoscopy

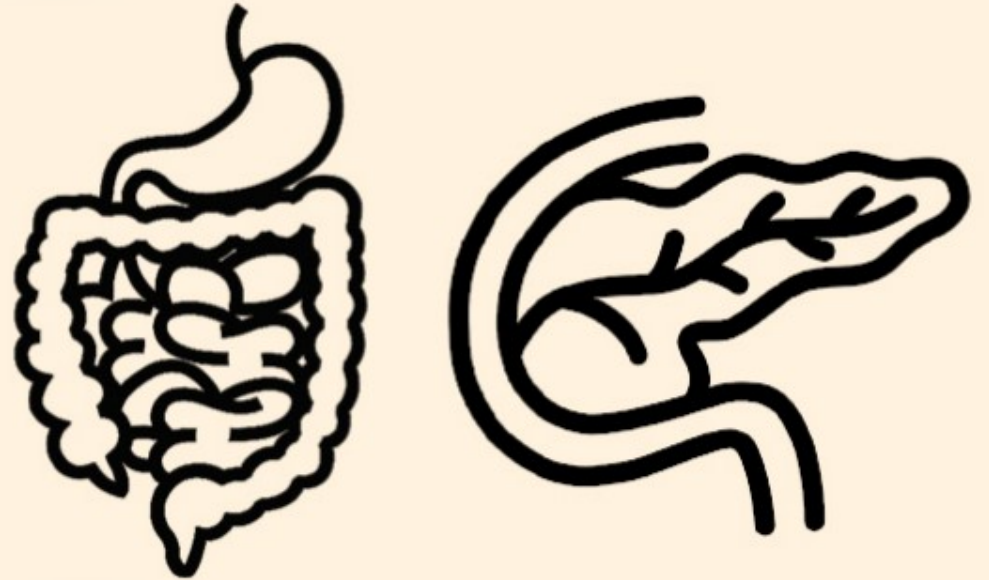
Diagnosis

Treatment

SITE OF ORIGIN

→ Wall-NETs

→ Pancreatic NETs



Gastroenteropancreatic NETs- Pancreatic NETs

Functioning and Non-functioning

❖ Functioning NETs

A functioning NET syndrome is defined by the presence of a clinical syndrome combined with biochemical evidence of inappropriately elevated hormonal levels.

TABLE 3 Overview of the different functional Pan-NET syndromes.

	Clinical features	Biochemical diagnosis	Alternative name
Insulinoma	Fasting hypoglycaemia	(Pro-)insulin, C-peptide during hypoglycaemia	Endogenous hyperinsulinaemic hypoglycaemia
Gastrinoma	Reflux, dyspepsia, ulcers, PPI-responsive diarrhoea	Fasting gastrin >10x URL & gastric pH ≤2	Zollinger-Ellison syndrome
Glucagonoma	Diabetes mellitus, necrolytic migratory erythema, deep venous thrombosis, depression, cheilitis/stomatitis, normocytic anaemia, weight loss, hypoaminoacidaemia, cardiomyopathy	Fasting glucagon >500 pg/mL	
VIPoma	Secretory diarrhoea, hypokalaemia, achlorhydria hypercalcaemia	Fasting VIP >60 nmol/L	Verner-Morrison syndrome
ACTHoma	Hypokalaemia, diabetes mellitus, muscle weakness, hypertension, moon facies, oedema	24 h urine cortisol, midnight salivary cortisol, cortisol after 1 mg dexamethasone overnight, ACTH	Ectopic Cushing's syndrome
PTHrPoma	Hypercalcaemia, hypophosphataemia, elevated alkaline phosphatase	PTH-rP >URL, Suppressed PTH	Humoral hypercalcemia of malignancy
Carcinoid syndrome	Diarrhoea, flushing, asthma, fibrosis	Urine 5-HIAA >50 µmol/24 h Elevated plasma 5-HIAA or serotonin	
Calcitoninoma	Diarrhoea, flushing	Calcitonin >> URL	
GHRHoma	Acral overgrowth, cardiomegaly	IGF-1 >2x URL GHRH >250 mg/L	Ectopic acromegaly
Somatostatinoma	Diabetes mellitus, diarrhoea, steatorrhea, cholelithiasis, hypo-/achlorhydria, weight loss, central hypothyroidism	Fasting somatostatin >> URL	

Gastroenteropancreatic NETs- Pancreatic NETs

Diagnostic Work-up

The Role of Endoscopic Ultrasound (EUS)

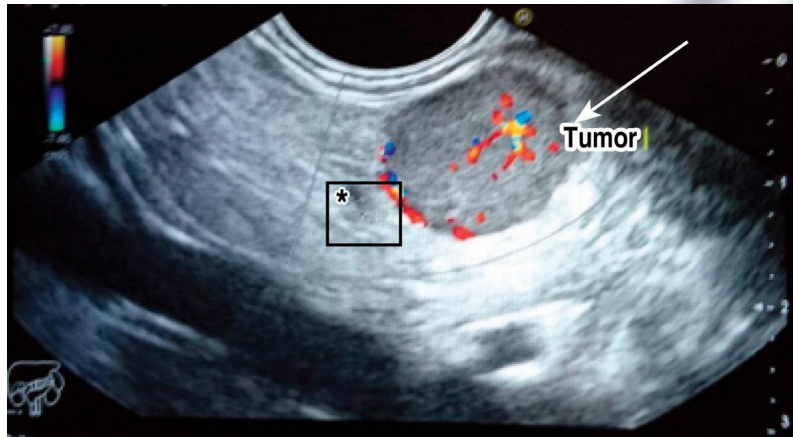
- ❖ Diagnostic sensitivity for combined CT and EUS: **100%**.
- ❖ **EUS alone:** sensitivity 87%, a specificity 98%, allows FNA biopsy/cytology, also for immunohistochemical staining of hormones.
- ❖ EUS can detect lesions as small as 2– 5mm.
- ❖ **EUS and MRCP** can provide the distance of the Pan-NET to the main pancreatic duct, which is crucial information for the possibility of performing an enucleation.
- ❖ **Duodenoscopy and EUS:** useful in the diagnosis of somatostatinoma of Vater's ampulla, associated with NF1, a nodular lesion of Vater's ampulla.



Gastroenteropancreatic NETs- Pancreatic NETs

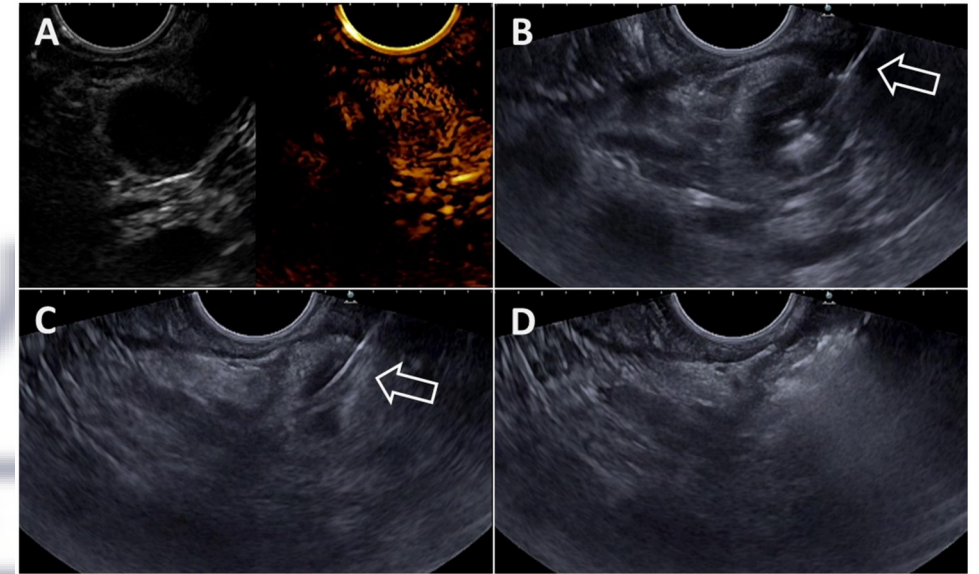
From EUS diagnosis to therapy

1. DETECTION



Small lesions • localization •
relationship with main
pancreatic duct

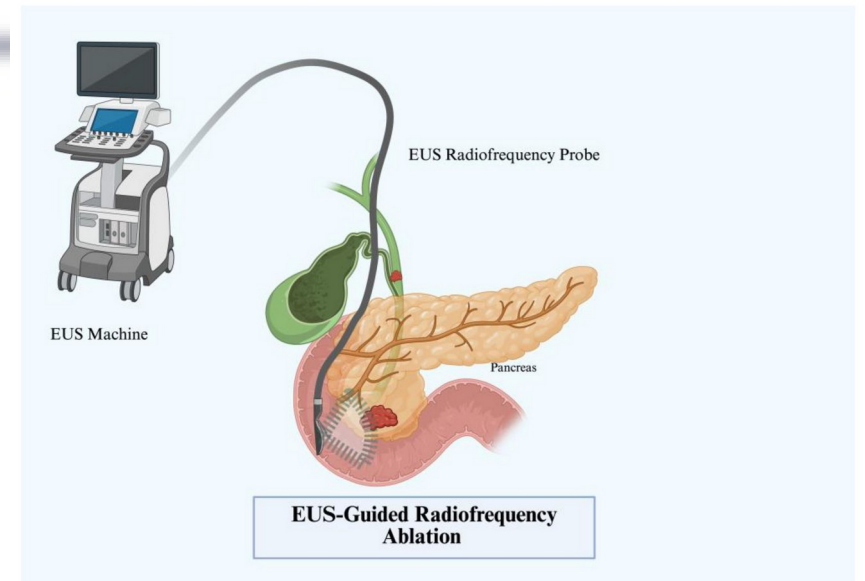
2. TISSUE ACQUISITION EUS-FNA / FNB



Diagnosis • grading • immunohistochemistry

3. TREATMENT EUS-guided RFA

EUS: detection →
characterization
→ tissue
acquisition →
selected local
therapy



Gastroenteropancreatic NETs- Pancreatic NETs

Therapeutic role of endoscopy in functioning Pan-NETs

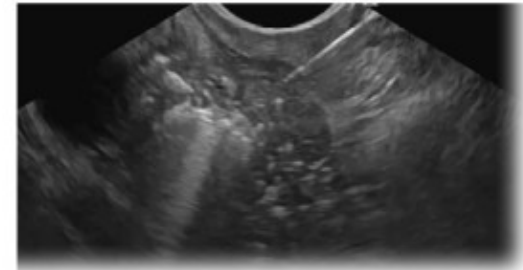
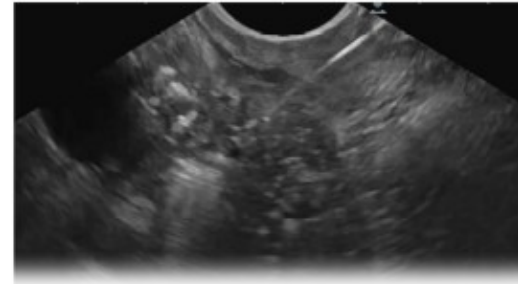
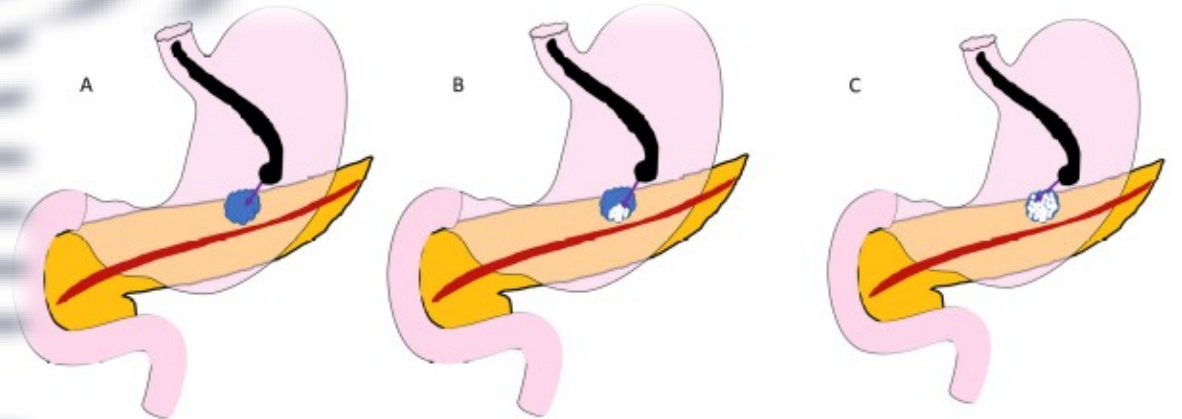
**EUS-guided radiofrequency ablation
(EUS-RFA)**

Induce necrosis of small pancreatic lesions



Indications:

- Small (≤ 2 cm) localised insulinomas;
- Patients unfit for surgery



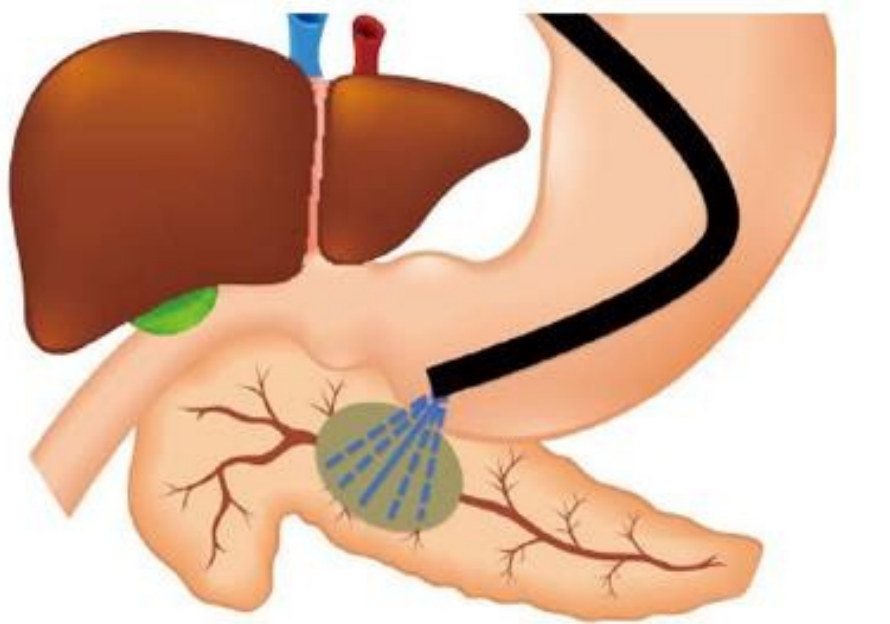
Gastroenteropancreatic NETs- Pancreatic NETs

❖ Non-functioning NETs

The diagnostic work-up follows the indications for pancreatic adenocarcinoma (localization, size, vascular involvement).



The Role of Endoscopic Ultrasound (EUS)



→ potentially resectable NF-Pan-NET :

- tumour size,
- vascular involvement,
- relationship to the main pancreatic duct,
- behaviour at dynamic contrast-enhanced EUS,
- EUS-guided sampling.

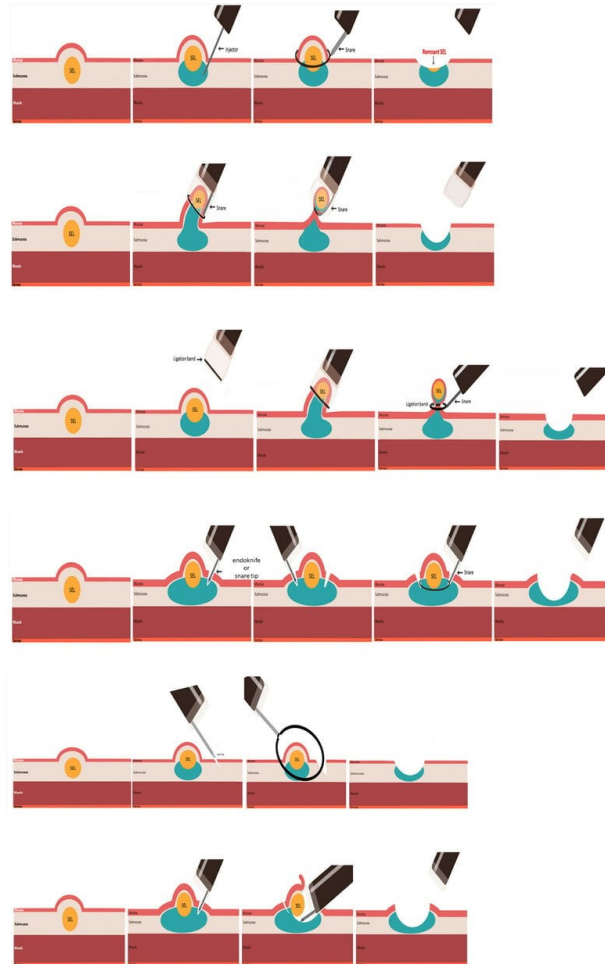
Gastroenteropancreatic NETs

Endoscopic resection techniques

EMR - mEMR - ESD - FTRD



Localized disease → target R0



GASTRIC NETs

Well-established role, depends on type (frequent for type I; selected cases for type III)

DUODENAL NETs

Possible for small lesions, safety-critical because the depth of resection must be targeted on the risk of perforation

SMALL BOWEL NETs

No role for endoscopy

COLONIC NETs

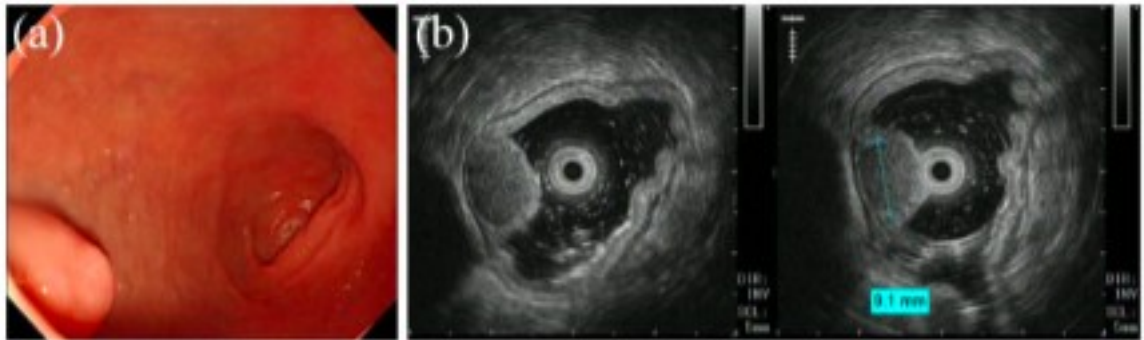
Limited and selected role for small G1 superficial lesions

RECTAL NETs

Wide comparative experience between endoscopic techniques.

Gastroenteropancreatic NETs

To establish endoscopic INDICATION →



EUS role: when there is the need to study the proximity to the muscularis propria

Risk stratification

1 Oncological risk (local disease)

- grade, Ki67
- LVI
- Distant metastasis, linfonodal involvement
- Functioning/nonfunctioning lesions

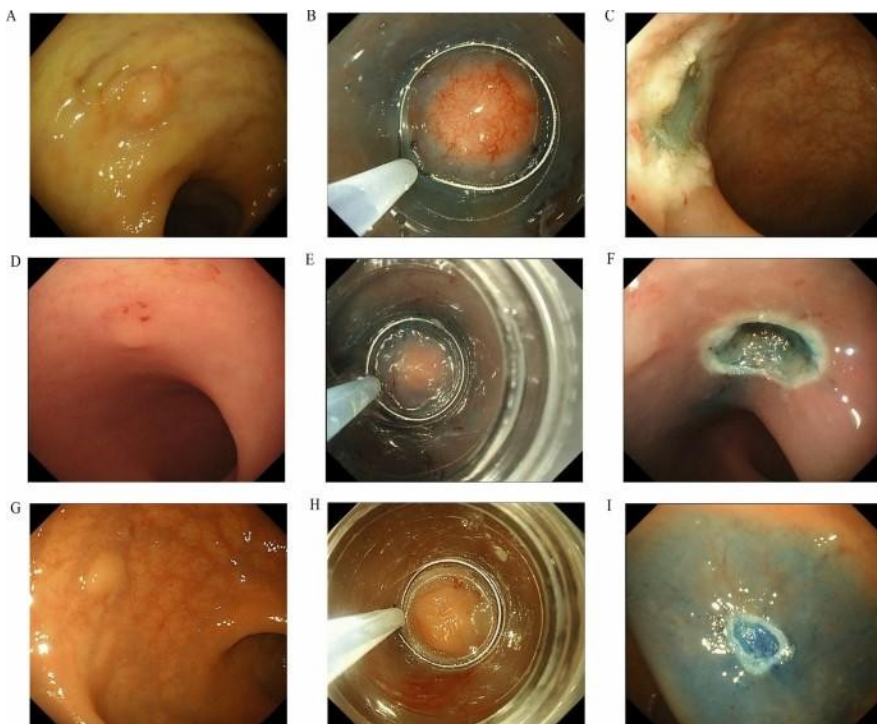
2. Depth

- Submucosal
- Muscularis propria

3. Endoscopic feasibility

- Size
- Localization
- Accessibility
- Proximity to other structures (ex. Papilla)
- Center expertise

Gastroenteropancreatic NETs – Endoscopic resection techniques

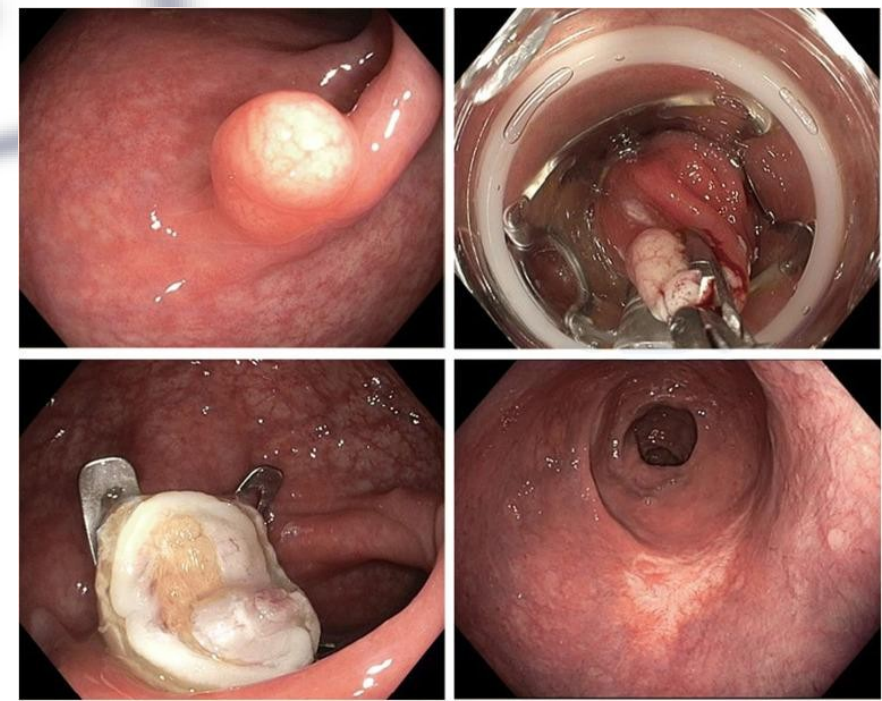
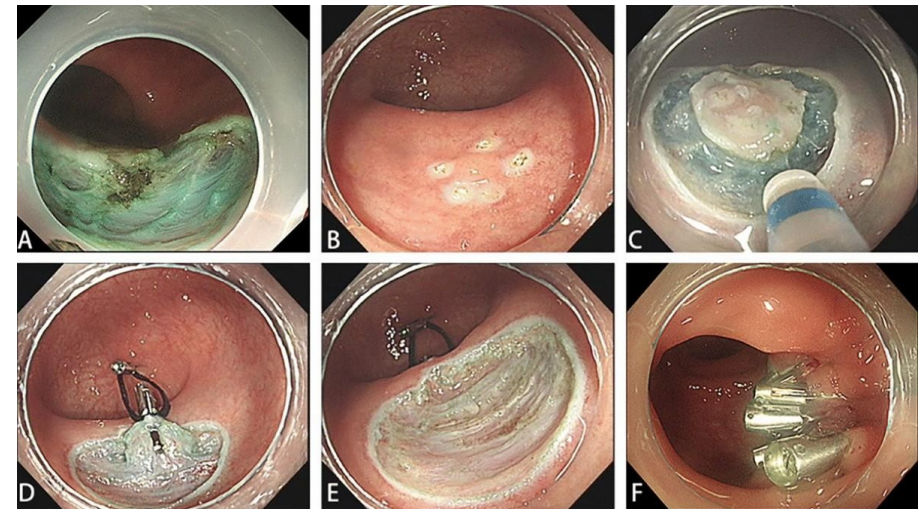


EMR
Lift → snare

Modified EMR
Suction → snare

ESD
Incision → dissection

FTRD / EFTR
Full-thickness
resection



***Different techniques, different control of the
deep margin!***

Gastroenteropancreatic NETs – Endoscopic resection techniques and adverse events

Adverse events: anatomy matters

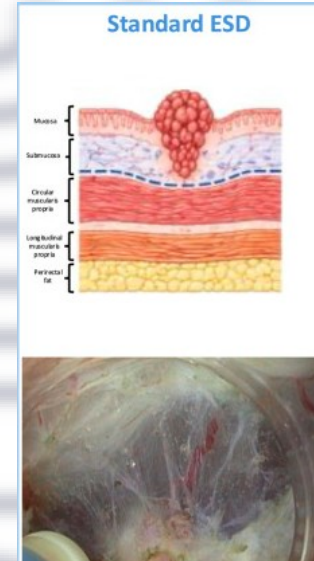
DUODENUM

- Perforation
- Delayed perforation
- Need for defect closure



RECTUM

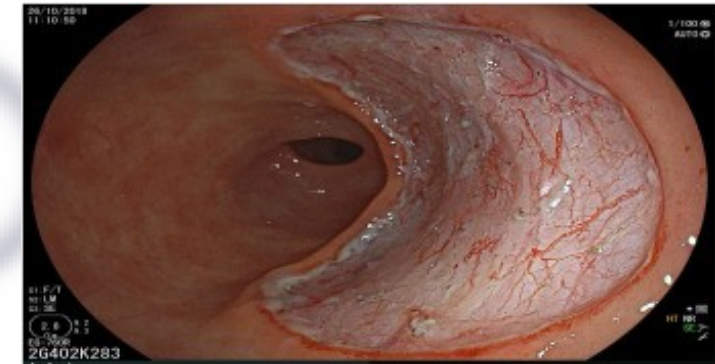
- Bleeding
- Perforation
Uncommon
- Deep resection
generally feasible



Clips → OTSC → endoscopic suturing

STOMACH

- Bleeding
- Perforation
- Advanced resection
generally feasible
in selected cases



The same depth of resection does not carry the same risk in every site!

Gastroenteropancreatic NETs – Gastric NETs

- **Type 1 gastric NET** – 70 to 80 percent of all gastric NETs, associated with chronic atrophic gastritis. Usually indolent.
- **Type 2 gastric NET** - 5 percent of gastric NETs, also occur because of elevated serum gastrin levels stimulating multifocal gastric NETs. Cause: pancreatic or duodenal gastrinoma (Zollinger-Ellison syndrome). Usually indolent.
- **Type 3 gastric NET** – sporadic, 20 percent of gastric NETs and the most aggressive; local or hepatic metastases are present in up to 65 percent of patients who come to resection.
- **●Type 4 gastric NET** – result from endogenous dysfunction of the parietal cell proton pump, linked in some cases to germline mutations of the *ATP4A* gene, which encodes the alpha-subunit of the proton pump. Patients typically have very high serum gastrin levels and innumerable small gastric NETs.
- **●Type 5 gastric NET** – Type 5 gastric NETs occur secondary to the chronic use of proton pump inhibitor.

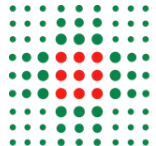
GASTRIC NETS: TYPES 1, 2, AND 3		
Type 1	Type 2	Type 3
		
Background: Autoimmune Atrophic Gastritis. High Gastrin. Benign course. Treatment: Observe/Resect.	Background: Zollinger-Ellison (MEN1). High Gastrin. Moderate risk.	Background: Normal. Normal Gastrin. Highly Malignant! Treatment: Radical Gastrectomy.

Gastroenteropancreatic NETs – Gastric NETs

Diagnostic Work-up:

- **Oesophagogastroduodenoscopy (OGD)** in virtual chromoendoscopy with biopsies of the tumour, the surrounding mucosa and other parts of the stomach (antrum and body-fundus) in order to determine aetiology, the prognosis and treatment of the NET.
- **Endoscopic ultrasound (EUS):** lesions >1 cm regardless of type; lesions of type III regardless of size, unless large or metastatic lesions are found.
- **Gastrin** assessment to differentiate between different types of gNETs. **CgA** is useful as tumour marker only in type III gNETs.
- Cross-sectional radiological imaging (**CT/MRI**) and **68Ga-SSA-PET- CT** are not required in type I gNETs, unless metastases on EUS or in the presence of high-risk features (G2, vessel invasion, suspected T2 on EUS).

Endoscopic appearance:



Gastroenteropancreatic NETs

- Gastric NETs

Endoscopic treatment: **I gNET**

1- type I gNETs > 1 cm
 2- lesions with increased Ki-67 (increased risk of metastases and progression).

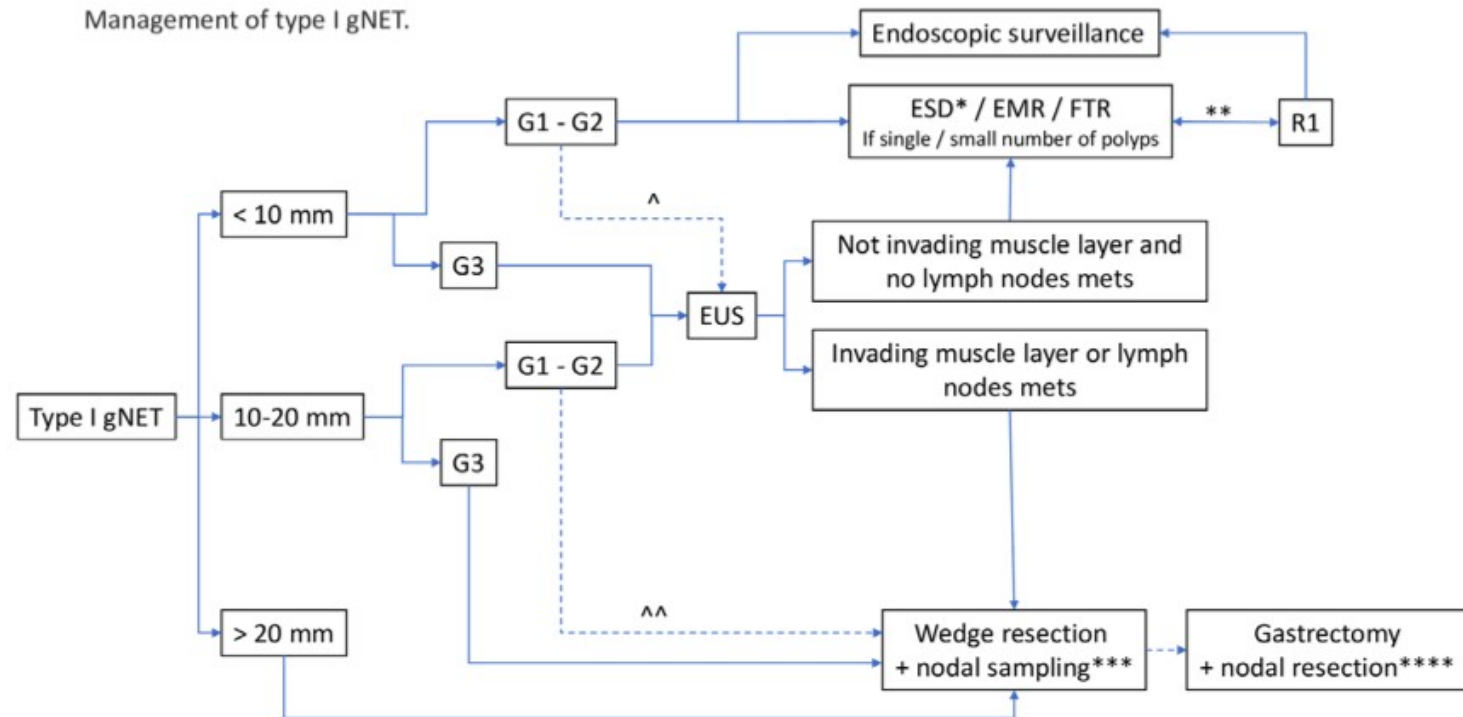
Resection technique of choice depends on:
size and position of the lesion, invasion depth and local experience.

EMR

ESD

FTRD

Management of type I gNET.



* ESD preferred vs EMR (lower risk of R1 margins after resection); ** ESD may be proposed in R1 cases after EMR. FTR may be proposed in R1 cases after ESD; *** Pre-operative staging with cross-sectional and functional imaging required; **** To be discussed in case of lymphatic spread after wedge resection

^ Consider performing EUS before endoscopic resection for high grade 2 NET (exact Ki67 not established); ^^ Consider surgical approach for high grade 2 NET (exact Ki67 not established)

EMR = endoscopic mucosal resection. ESD = endoscopic submucosal dissection. EUS = endoscopic ultrasonography. FTR = full-thickness endoscopic resection

FIGURE 1 Management of type I gastric neuroendocrine tumours (gNETs).

Gastroenteropancreatic NETs – Gastric NETs

I gNET

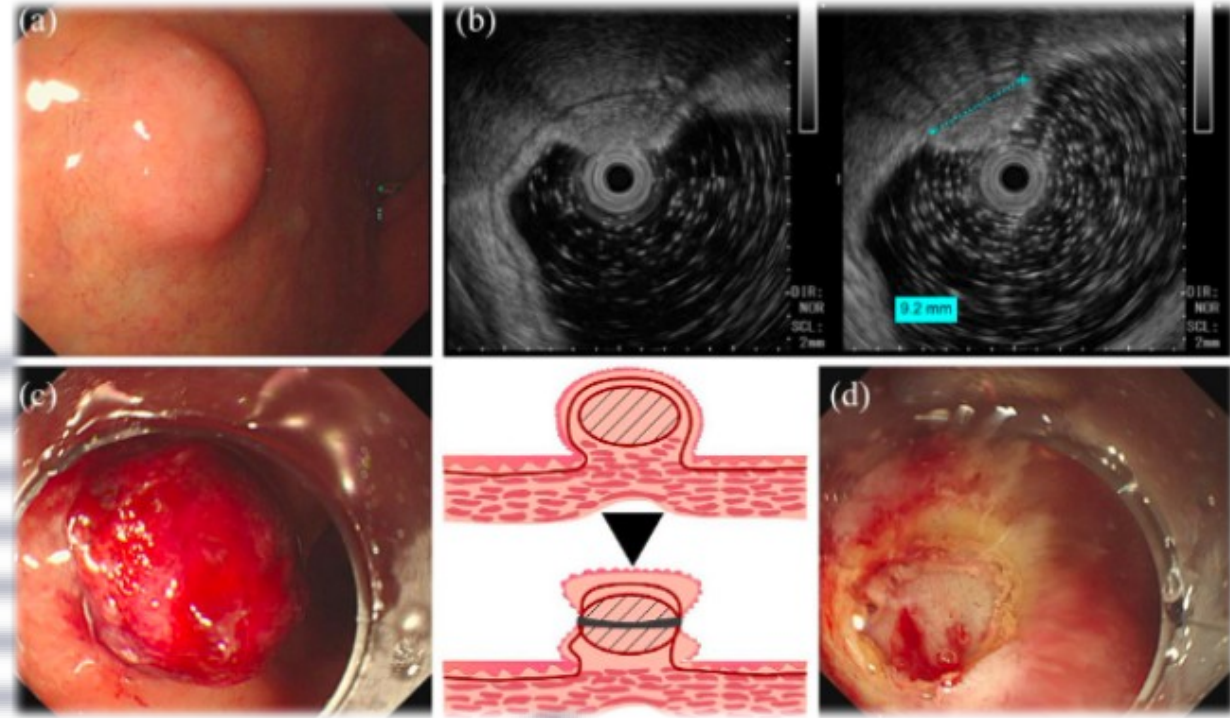
Conclusion/recommendations

1. Endoscopic resection should be proposed in type I gNETs larger than 1 cm (2b-A).
2. ESD and FTR are more effective to achieve R0 resection compared to EMR (2b-B).
3. In case of incomplete resection (R1) of a NET >1 cm a step-up approach (EMR > ESD > FTR > surgery) is recommended (4-C).

CLINICAL GUIDELINE

Journal of Neuroendocrinology WILEY

European Neuroendocrine Tumor Society (ENETS) 2023
guidance paper for gastroduodenal neuroendocrine
tumours (NETs) G1–G3



Endoscopic Follow-up after resection:

- OGD is recommended 12 months after complete endoscopic resection.
- In those not requiring resection first follow-up should be 12 months and then consider annual to every 1–2 years.
- In patients with type I gNET, endoscopic follow-up by OGD is recommended also given the risk of developing gastric adenocarcinoma related to CAG.

Gastroenteropancreatic NETs

– Gastric NETs

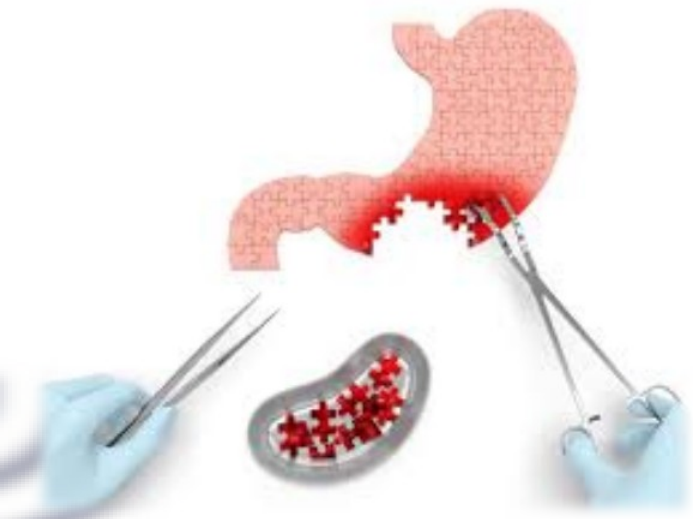
II gNET: treatment of patients with type II gNETs strictly depends on the management of the MEN-I syndrome.

III gNET: traditionally only surgical indications, but with HD-endoscopy smaller and lower grade lesions can be evaluated for **endoscopic treatment**

EMR or ESD

Follow-up

- *R1 resections should be considered for other endoscopic resection or surgery*
- *OGD after 3 month then regular FU with CT/RM or EUS*



1- no evidence of lymph node involvement
2- localised G1 tumours ≤ 10 mm in diameter
3- can be considered in patients with lesions < 15 mm and low G2 (Ki-67 3–10%) histology, particularly if the risks of surgical resection are considered to be high.

Gastroenteropancreatic NETs

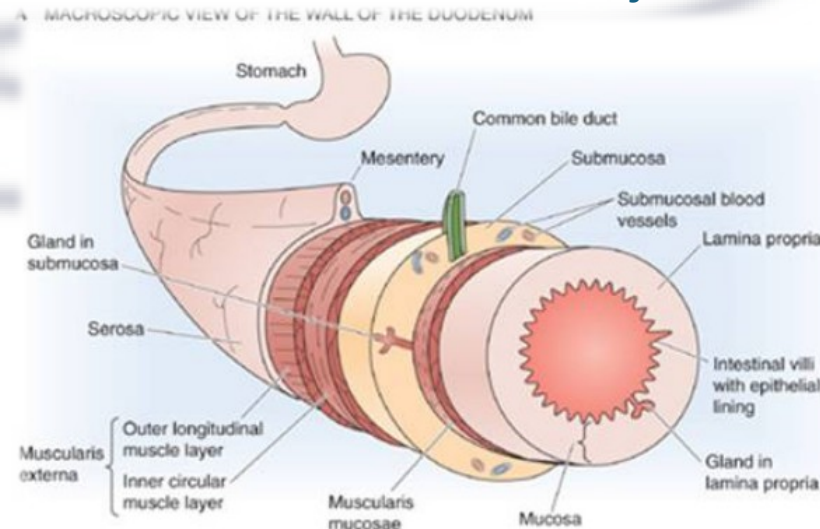
– Duodenal NETs

Endoscopic role:

- Diagnosis (similar to gNETs, single small sessile, erythematous or pale lesions in the duodenal cap, bulb or D1 to D2) confirmed by biopsies;
- Evaluation of proliferative activity of the tumour (Ki-67 and/or mitotic count) for grading (on biopsy or ago-biopsy);
- Lesions >1 cm must be studied with EUS;
- **Resection of the lesion**

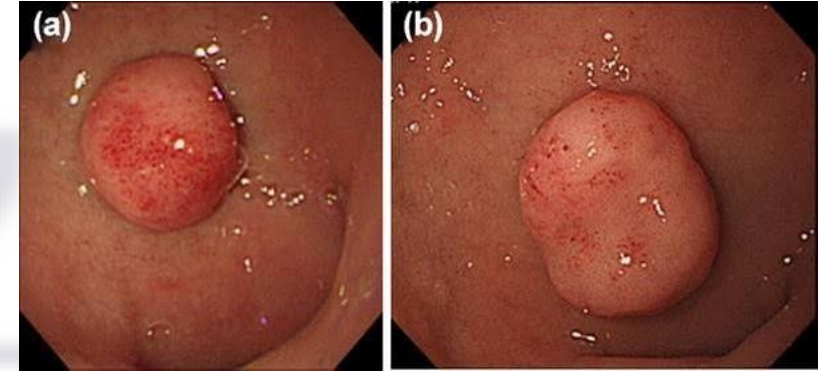
Main Features:

- Rare (2.8% of total NETs), increasing as incidental discovery during OGD or CS imaging;
- Can be associated to MEN-I and neurofibromatosis type 1 (NF1);
- dNETs are functioning or non-functioning tumours (CogNET, duodenal gastrinoma, duodenal NEC);
- Usually found in the first or second part of duodenum;
- Symptoms range from none to GOO or anemia;
- Peri-ampullary lesions (NF1) can present with gastrointestinal bleeding, abdominal pain, anaemia or jaundice



Gastroenteropancreatic NETs – Duodenal NETs

A watch and wait policy could be considered for very small (<5 mm) dNETs that cannot easily be resected, are non-functional, G1 and not invading the muscularis propria. This policy has usually been applied in patients unfit for endoscopic resection or surgery



Management strategy:

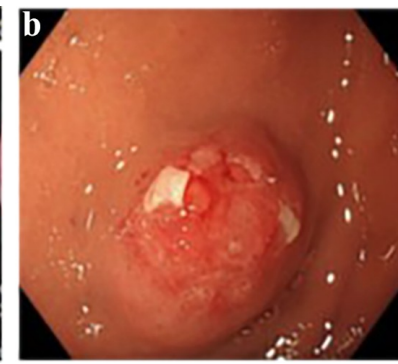
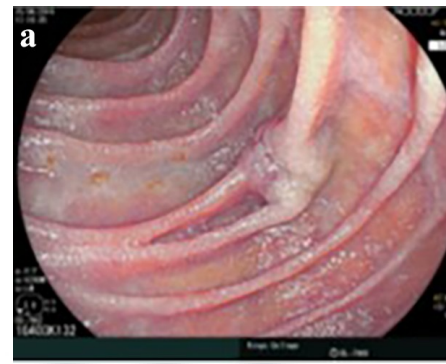
1. Size of tumour;
2. Number or lesions (duodenal NET can be multifocal);
3. Depth of invasion in relation to the deep muscle layer;
4. Any evidence of lymphadenopathy and/or metastatic spread on EUS, liver-MRI, thoracoabdominal CT and functional imaging, preferably 68Ga-SSA-PET-CT;
5. Grade and morphology of tumour;
6. Endoscopic appearance: central depression/ulceration implies invasion;
7. Suitability for endoscopic resection: size of lesion/endoscopic access/location of lesion/proximity to ampulla;
8. Hormone secretion status;
9. Patient age and performance status.

Very small non-functioning tumours in D1 should be removed using EMR type techniques

Lesions of 5–10 mm (and up to 15 mm in some centres) can be removed endoscopically after imaging work-up, but risks are relatively high

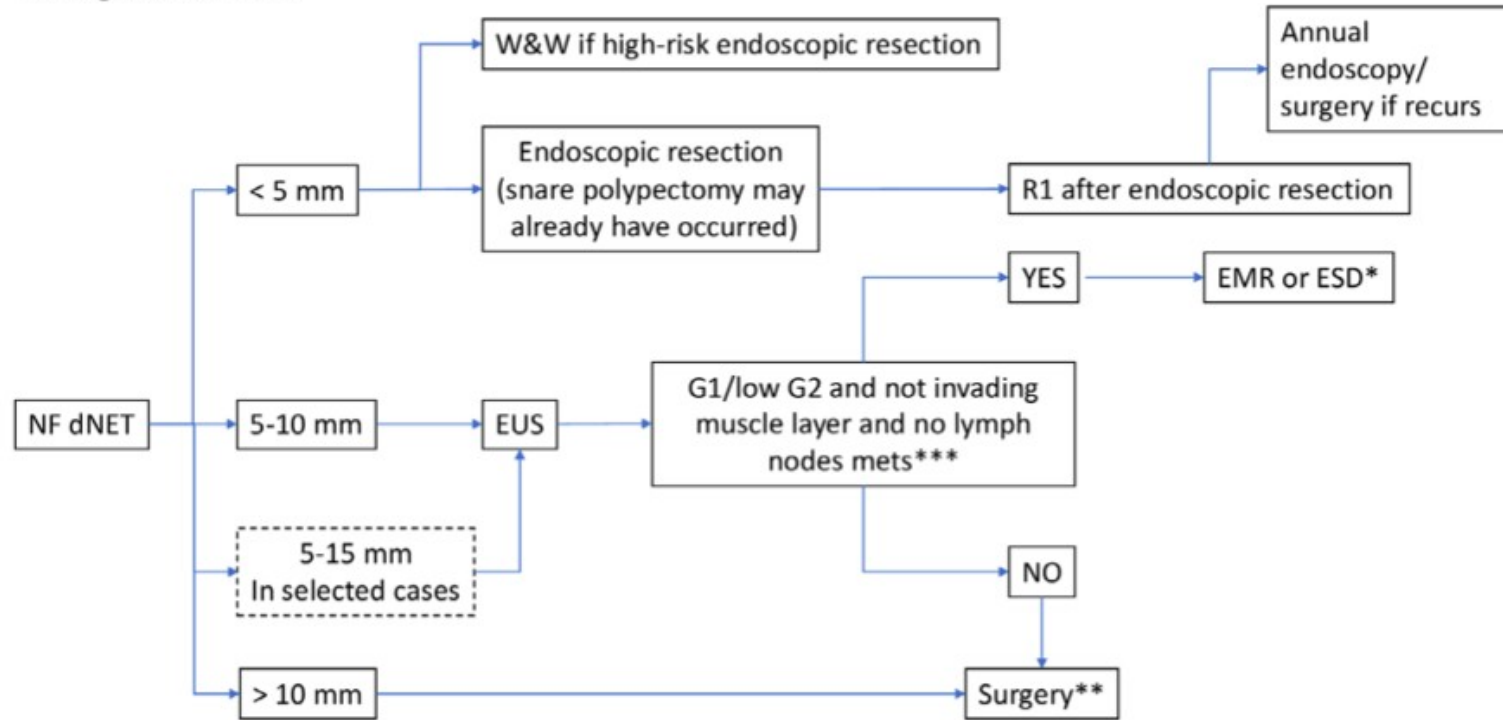
Gastroenteropancreatic NETs

- Duodenal NETs



Choice of endoscopic technique

Management of dNET.



* ESD: only in centers with specific experience in advanced endoscopy (consider the high risk of duodenal perforation)

** Pre-operative staging with cross-sectional and functional imaging required.

***Endoscopic appearances of ulceration/ rolled edges may also indicate risk of invasion

W&W: watch and wait endoscopic surveillance; EMR: endoscopic mucosal resection; ESD: endoscopic submucosal dissection

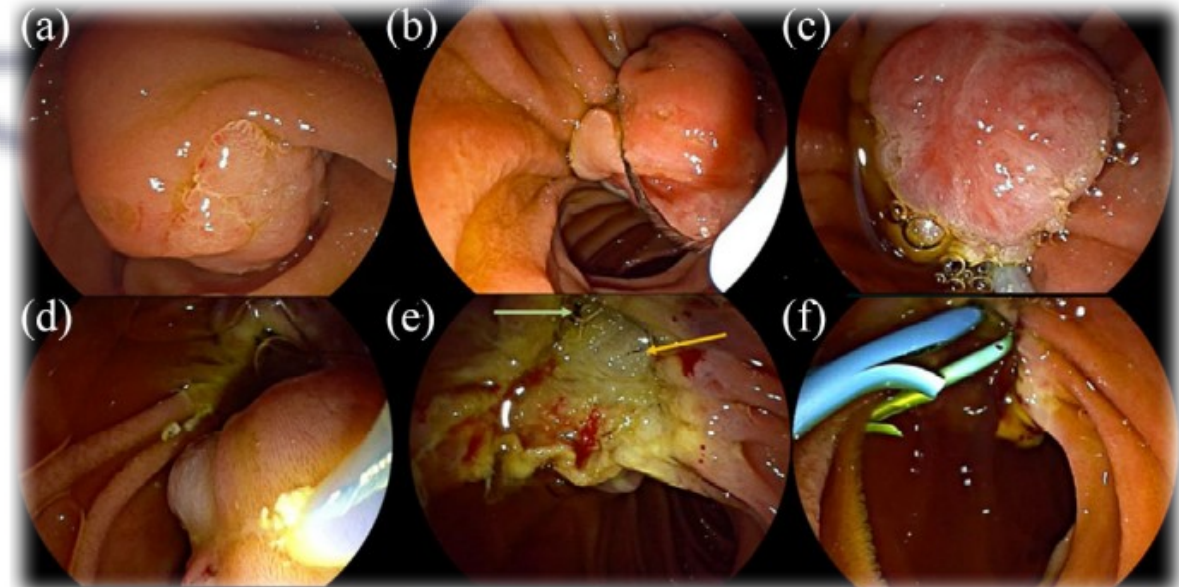
Gastroenteropancreatic NETs

– Ampullary NETs

- ❖ Extremely rare lesions: less than 1% of all gastrointestinal NETs and under 2% of all periampullary cancers.

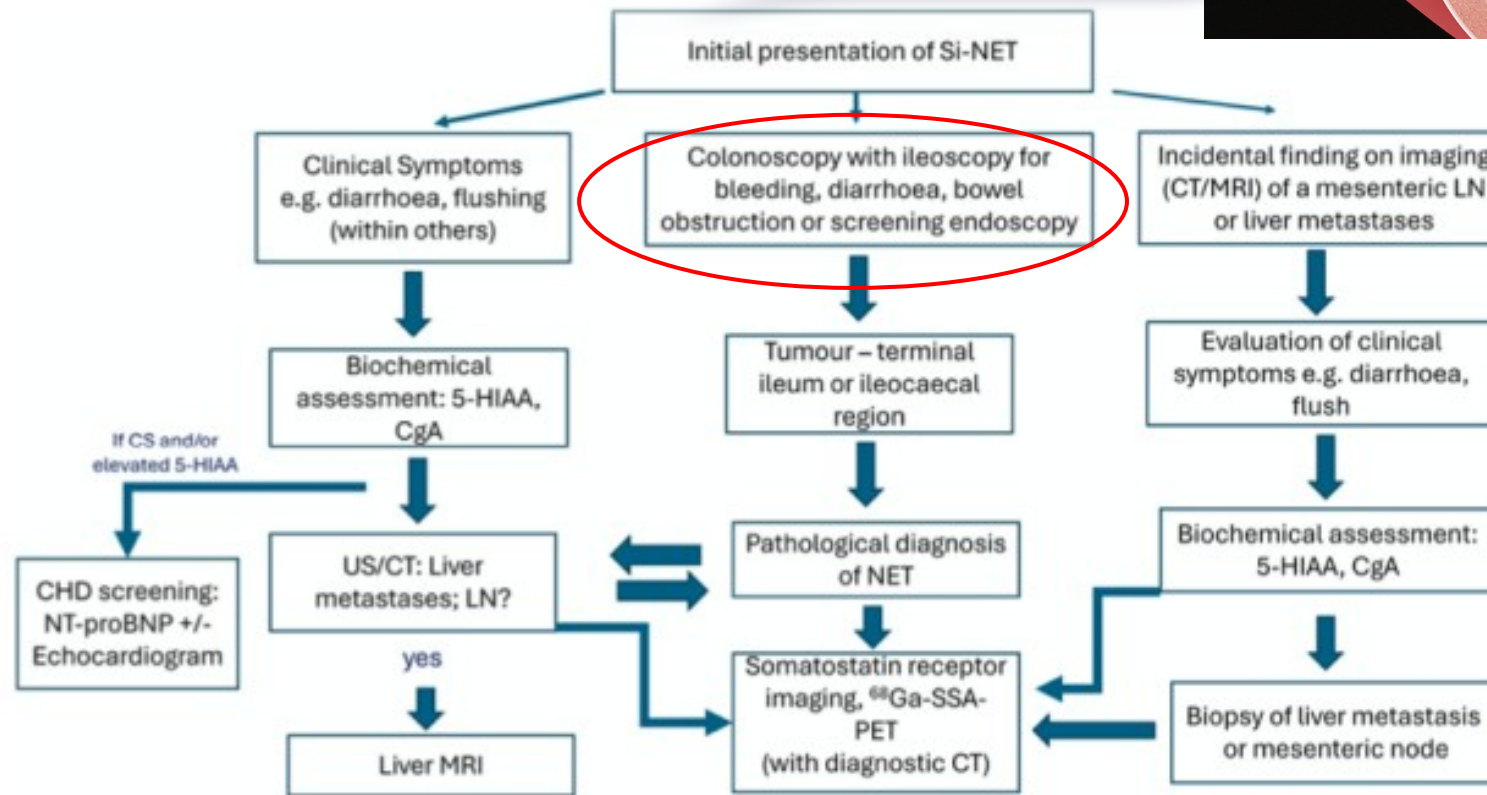
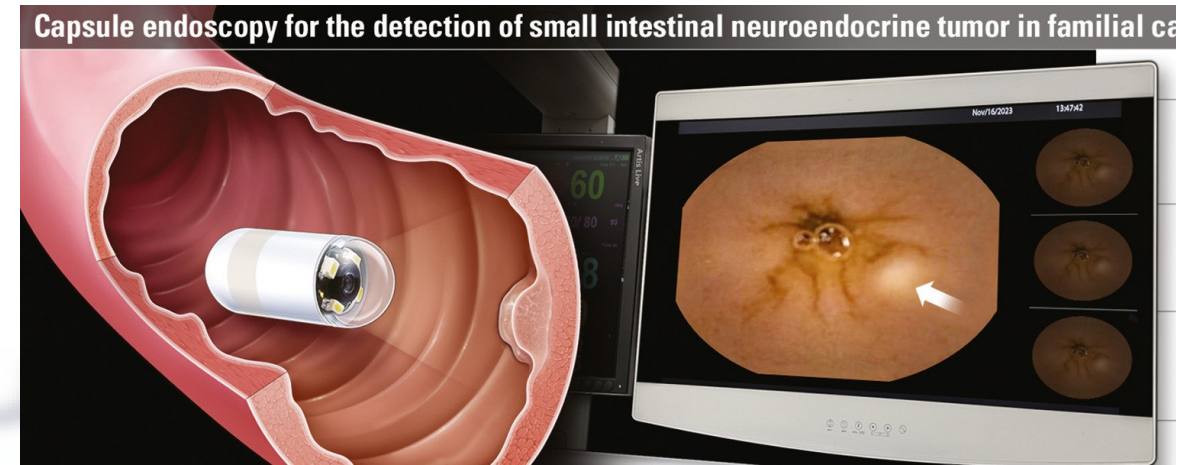
Standard Treatment: The ENETS guidelines recommend pancreaticoduodenectomy (the Whipple procedure) as the primary surgical approach due to the risk of aggressive behavior and lymph node involvement.

Alternative Options: For very small tumors (typically under 2 cm) without lymph node spread, or for patients with severe medical conditions, less invasive methods like endoscopic papillectomy (EP) or surgical ampullectomy are emerging as viable, selective alternatives.



Gastroenteropancreatic NETs – Well-differentiated small intestine NETs

Endoscopic role in the diagnostic work-up



Usually an incidental finding during capsule endoscopy study

FIGURE 1 Diagnosis of Si-NET.

Gastroenteropancreatic NETs

– Colorectal NETs

Right colon NETs



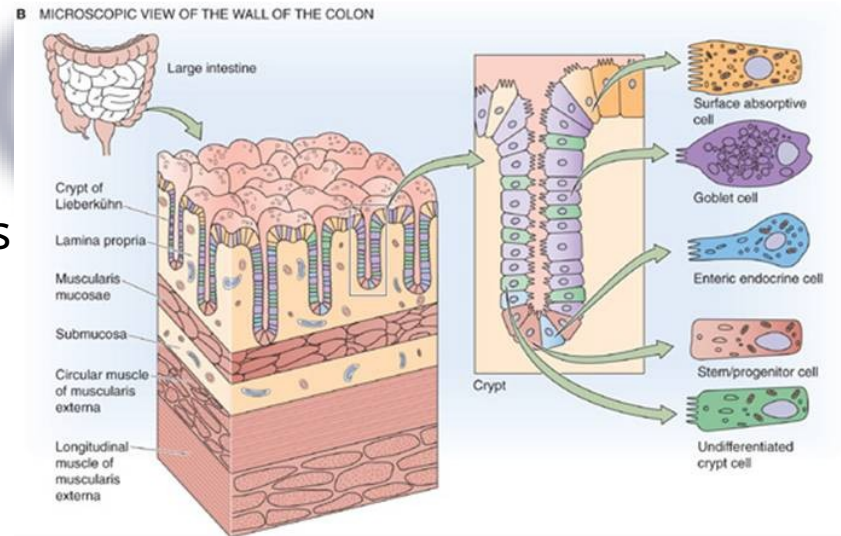
Midgut tumors → ileal NETs

Left colon NETs



Hindgut tumors → rectal NETs

- Usually single lesions;
- Large;
- Highly invasive;
- G3 more frequent than ileal NETs



Gastroenteropancreatic NETs

– Colorectal NETs

Endoscopic resection of colonic NETs

- Selected cases, small (usually 10 mm or less) colonic NET G1.
- MDT discussion is recommended for the FU;
- Surgical resection for any other case and endoscopic R1.

Factors associated with worse outcomes for colorectal neuroendocrine tumors in radical versus local resections

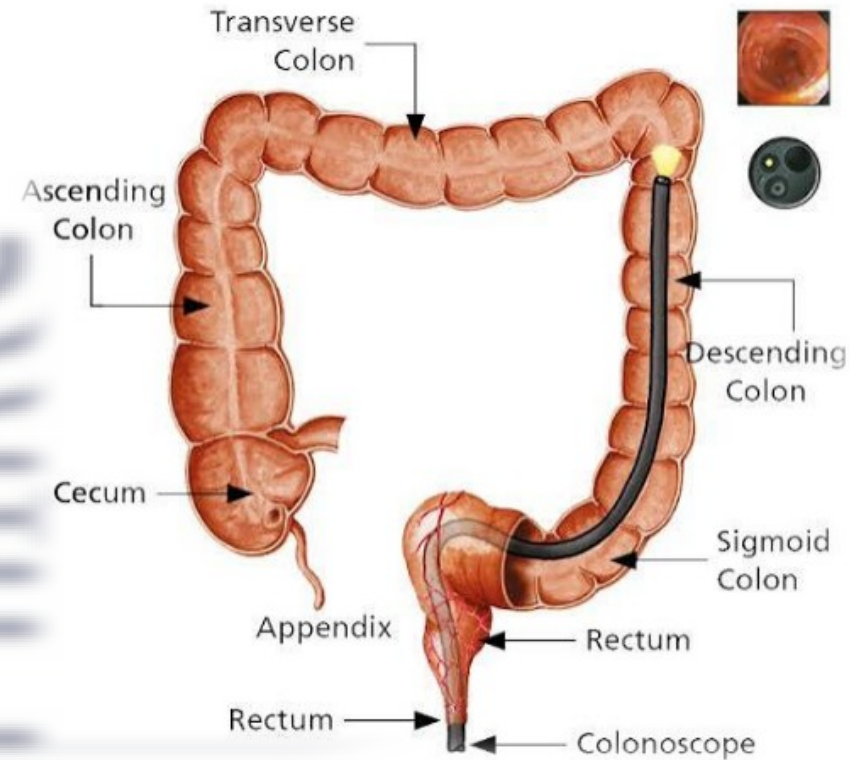
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Contributions: (I) Conception and design: O Osagiede, E Haberman, D Colibaseanu; (II) Administrative support: E Habermann, D Colibaseanu; (III) Provision of study materials or patients: E Habermann, E Gabriel; (IV) Collection and assembly of data: O Osagiede, E Habermann, C Day; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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J Gastroenterology Oncology, 2020

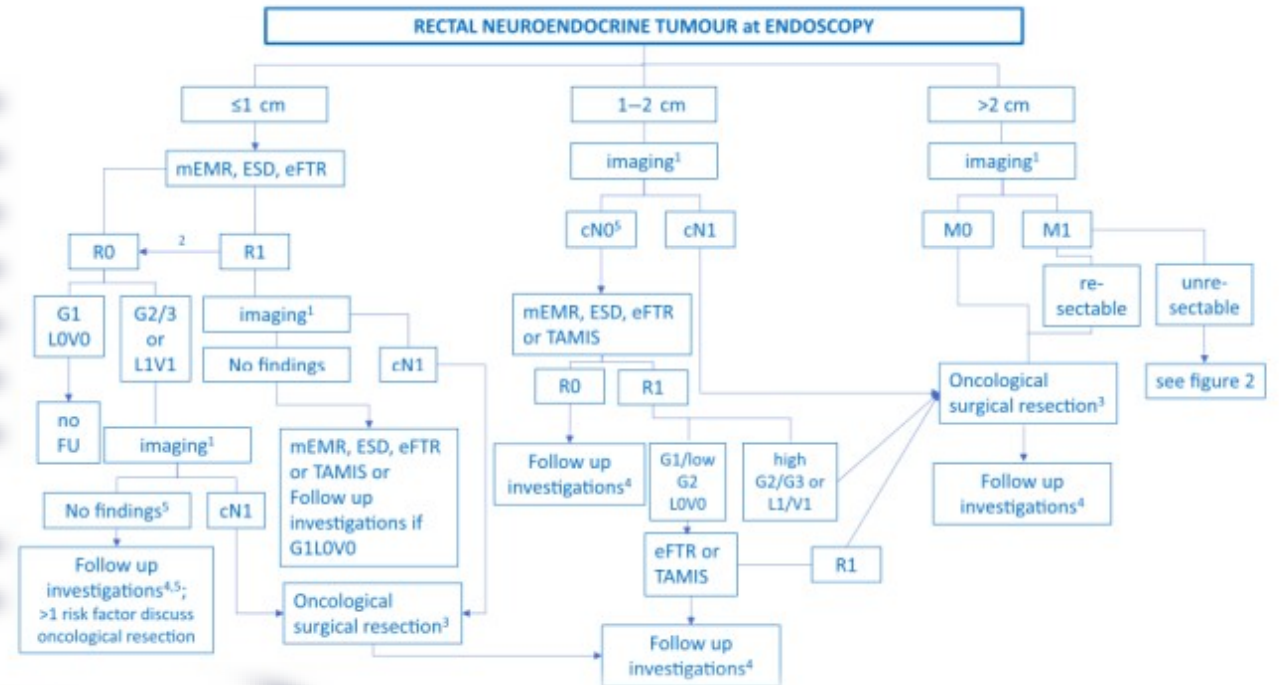


- Resection of 7967 colonic and 11,929 rectal NET between 2004 and 2014;
- 525 (6.6%) colon NET 89.1% rectal NET;
- **Key findings: endoscopic excision for colonic NET is increasing over time as stage and tumour size are reducing.**

Gastroenteropancreatic NETs – Colorectal NETs

Rectal NETs

1. Simple polypectomy
2. Endoscopic mucosal resection (EMR)
3. Cap-EMR
4. Underwater EMR
5. Endoscopic submucosal dissection (ESD)
6. Transanal minimally invasive surgery (TAMIS) or transanal endoscopic microsurgery (TEMs).
7. Low anterior resection (LAR) with total mesorectal excision (TME)
8. Abdominoperineal resection (APR) with TME



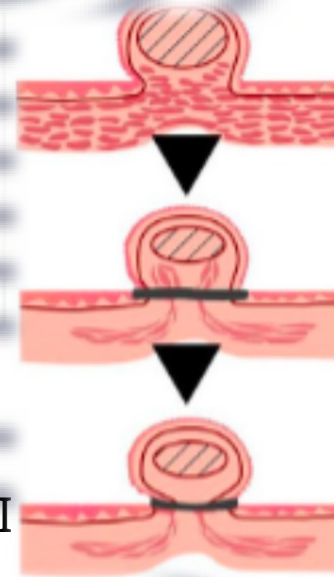
Gastroenteropancreatic NETs

– Colorectal NETs

Rectal NETs

Recommendations (post R1 resection)

- **>2 cm or adverse features** (higher G2 / G3; L1; V1): oncological resection after exclusion of distant metastases
- **1–2 cm** full imaging and endoscopic work up. Repeat endoscopic resection if appropriate (full thickness)
- **<1 cm**. Ideally: Second endoscopic resection or TAMIS to achieve R0, alternatively: if negative EUS, MRI and repeat biopsy: watch and wait after discussion with patient.



Gastroenteropancreatic NETs

– Colorectal NETs

Follow-up

- After **R0** resection of a **rectal NET G1 L0 V0 ≤ 10 mm**: NO FU
- After **R0** resection of a **rectal NET G1 L1 or V1 or G2/G3 ≤ 10 mm**: MRI after 6 month, yearly sigmoidoscopy for at least 5 years, ^{68}Ga -SSR-PET/CT initially and after 12 months.
- After **R1** resection of a **rectal NET G1/ low G2 ≤ 10 mm** (without second endoscopic resection to reach R0): endoscopy and EUS or MRI 12 monthly for at least 5 years.
- After **R0** resection of a **rectal NET G1/G2 > 10 mm**: MRI after 6 month and yearly sigmoidoscopy for at least 5 years, ^{68}Ga -SSR-PET/CT initially and after 12 months.
- After **R0** resection of a **rectal NET G3**: MRI every 3 month for 2 years, then every 6 month for 5 years, sigmoidoscopy every 6 month for 2 years, followed by yearly endoscopic investigations for 5 years. ^{68}Ga -SSR-PET/CT initially and after 12 months. Consider ^{18}F -FDG PET/CT.

Gastroenteropancreatic NETs

Take-home messages

01

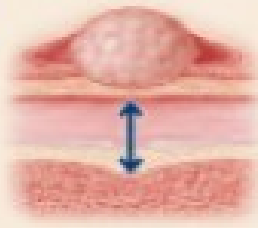


INDICATION

Patient and tumour selection comes first.

Endoscopic R0 is meaningful only in appropriately selected localized disease.

02



DEEP MARGIN

En bloc ≠ R0.

NETs are mainly submucosal lesions: the vertical margin matters.

03



TECHNIQUE

mEMR captures ·
ESD dissects ·
EFTR includes muscle.

There is no universal hierarchy between techniques.

04



SITE

The appropriate depth depends on anatomy.

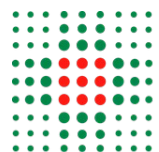
Rectum ≠ stomach ≠ duodenum.



The best technique is not the deepest one,
but the one that reaches the required plane with an acceptable risk.



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